REMARKS

I. Status of the Claims

Claims 1-7, 9-15, 29-31, 33, and 34 will be pending in this application after the instant amendments are entered. Claims 16-28 and 32 had been previously cancelled. Claim 1 has been amended to incorporate the subject matter recited in claim 8, now cancelled. In addition to finding support in original claim 8, the amendment also finds support in the as-filed specification at page 9, ll. 28-31. Claims 9-11 have been amended to depend from claim 1 in light of the cancellation of claim 8, from which they previously depended. New claim 34 finds support, throughout the specification, for example at p. 4, line 5 to p. 5, line 19, which describe non-charged components of the membrane. Accordingly, no new matter is added with these claim amendments.

II. Rejections under 35 U.S.C. § 102(e) or under 35 U.S.C. § 103(a)

A. *Kim and Gorsuch*

The Office rejects claims 1, 3-10, and 12-13 under 35 U.S.C. § 102(e), as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent Application Publication No. 2004/0167237 to Kim et al. ("*Kim*") as evidenced by U.S. Patent No. 6,802,820 to Gorsuch et al. ("*Gorsuch*"). Office Action, pages 2-3. The Office contends that "Kim discloses an asymmetric hollow fiber membrane . . . comprised of at least one hydrophobic polymer and at least one hydrophilic polymer . . . wherein said membrane allows passage of molecules having a molecular weight of up to 45kD with a sieving coefficient of 0.1-1.0 in the presence of whole blood, wherein the membrane allows the retention of a portion of albumin in the presence of whole blood." *Id.*, page 2.

The Office acknowledges that "Kim is silent as to the molecular weight exclusion limit of about 200kD," but argues that since "Kim discloses a hollow fiber membrane with the same preferred structure as contained in Applicant's claims/specification . . . it is inherent that said membrane has the molecular weight exclusion limit." *Id.* The Office alternatively asserts "that size exclusion limits and sieving coefficients can be easily manipulated based on test methods used to determine the size exclusion limits and sieving coefficients . . . [and that] it would have been obvious to modify the molecular weight exclusion limit of Kim since [molecular weight exclusion limits are deemed to be result effective variables as evidenced by Gorsuch]." *Id.* Applicants respectfully disagree and traverse this rejection for the reasons outlined below.

1. *Kim* does not explicitly nor inherently anticipate the membrane recited in the instant claims

The Office argues that *Kim* discloses a membrane that "allows passage of molecules having a molecular weight of up to 45kD with a sieving coefficient of 0.1-1.0 in the presence of whole blood, wherein the membrane allows the retention of a portion of albumin in the presence of whole blood." Office Action, page 2. However, *Kim*'s sieving coefficients and molecular weight cutoffs listed in Table I were not measured in blood, but rather measured in saline solutions. *Kim* at ¶ [0188] (indicating that the fiber obtained in Example 1 was evaluated according to the method in ¶ [0157], which does not involve measurements in whole blood). Thus, the Office's assertion that these claim elements are met by *Kim,* is incorrect. Because *Kim* fails to disclose the instantly-recited values for the molecular weight cutoffs and sieving coefficients of its membrane in whole blood, *Kim* does not anticipate the presently claimed membrane. A rejection

under § 102 is proper only when the claimed subject matter is identically described or disclosed in the prior art. *In re Arkley*, 455 F.2d 586, 587,172 U.S.P.Q. 524, 526 (CCPA 1972); *see also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989).

While the Office concedes that *Kim* fails to disclose all the claimed elements ("molecular weight exclusion limit") in a single embodiment, thus failing to pass the proper test under 102 (*see e.g., Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989); *Connell v. Sears Roebuck & Co.*, 722 F.2d 1542, 1548, 220 U.S.P.Q. 193, 198 (Fed. Cir. 1983)), the Office implies that the omitted elements in *Kim* are inherently disclosed. Applicants disagree.

The proper standard for inherent anticipation requires that "the prior art necessarily functions in accordance with, or includes, the claimed limitations," regardless of whether persons of ordinary skill in the art would "recognize the inherent characteristics or functioning of the prior art." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (citing *In re King*, 801 F.2d 1324, 1326, 231 U.S.P.Q. 136, 138 (Fed. Cir. 1986). In order to rely on such a theory of inherency, the Office must provide a basis in fact and/or technical reasoning to support the assertion that the allegedly inherent characteristic necessarily flows from the teachings of the prior art. M.P.E.P. § 2112(IV).

Here, the Office fails to provide sufficient factual and technical reasoning to establish that the inherent features (*e.g.*, wherein said membrane allows passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 in presence of whole blood, and has a molecular weight exclusion limit of

about 200,000 Daltons and wherein the membrane allows the retention of a portion of albumin in the presence of whole blood) flows from the teachings of *Kim*.

As discussed above, *Kim* fails to teach sieving coefficients and molecular weight cut offs for its membrane in whole blood. Even assuming that *Kim*'s sieving coefficients and molecular weight cut offs disclosed in Table I were measured in whole blood, they still would not anticipate the claimed sieving coefficients and weight cut off limits because *Kim*'s membrane is fundamentally different than the presently claimed membrane.

a. *Kim's* reported molecular weight cut-off values and sieving coefficients do not correspond to the values recited in the instant claims

Kim teaches that its membrane has a molecular weight cut-off of 40±5 kD. That is, molecules having a molecular weight of 45kD will be "cut off" form the membrane and *will not pass through the membrane*. *Kim* at Table 1. In contrast, the instantly-claimed membrane allows for passage of molecules having a molecular weight of up to 45kD with a sieving coefficient of 0.1-1.0 in presence of whole blood. Thus, where *Kim*'s membranes fully retain molecules with a molecular weight of 45kD (or higher), the presently-claimed membrane allows their passage with a sieving coefficient ranging from 0.1-1.0 in whole blood. That is, a molecule with a molecular weight of 45kD will pass through the instant membrane at least 10% (sieving coefficient of 0.1.)

Albumin demonstrates the distinction between *Kim's* membrane and the membrane of the instant invention for molecules having a molecular weight higher than 45 kD. For example, *Kim* demonstrates that albumin, with a molecular weight of approximately 67kD (see *Kim* at ¶ [0019]), is retained within *Kim*'s membrane. *Kim* at

¶ [0201] ("leaking of albumin was considerably suppressed and fractionation performance was improved due to static repulsion of introduced negative charges"). Thus, *Kim*'s membranes suppress leakage of albumin, which is indicated in the relatively low sieving coefficient for albumin (.0004 and .0005) listed at Table I, and which, according to *Kim*, represents an improvement upon comparative membranes with sieving coefficients for albumin ranging from 0.006 to 0.011, that "leaked much albumin, resulting in low fractionation performance." *Kim* at comparative examples 1-3; ¶ [0200]. *In other words,* Kim *not only discloses a membrane different from the instant membranes, but also teaches away from a membrane that allows the passage of albumin because even a sieving coefficient of 0.011 is considered to "leak much albumin."*

In contrast, membranes according to the present invention allow the passage of molecules in the range of 45 kD to the extent instantly claimed, and also allow the passage of a portion of albumin (i.e., at least some albumin is not retained in the membrane). *See, e.g.*, specification at paragraphs [020] and [048] of the published version of the application (US2006/0144782). This behavior is also supported by the Declaration under 37 C.F.R. §1.132 of co-inventor Hermann Goehl ("Declaration") submitted August 20, 2010. Table I (page 5) of the Declaration indicates that a membrane in accordance with the invention has a sieving coefficient for albumin of at least 0.1 (10%) and 0.11 (Figure 1), which is 10 to 100 times higher that the sieving coefficients shown for albumin in Table 1 of *Kim*. Thus, contrary to the Office's assertion, *Kim*'s membranes are fundamentally different than the presently claimed membranes.

b. The separating layer in *Kim's* membrane is different from the separating membrane in the instant membranes

The outermost layer in *Kim's* membrane, the "dense layer free from electrical charges" functions as the separating layer. *Kim* at ¶¶ [0102] and [0215]. In contrast, the separation layer of the presently claimed membrane is found in the innermost layer of the hollow fiber and is not the outermost layer as in *Kim*'s membranes. *See e.g.*, originally-filed specification at page 9, ll. 28-31 (feature incorporated into claim 1 in the instant amendments).

c. Other properties of *Kim's* membranes evidence a structure different from the structure of the instant membranes

Moreover, *Kim*'s membranes have a "double barrier structure, one a size barrier and the other a charge barrier of negative charges," that "exhibit[] remarkably improved performance to separate a solute and/or dispersoid from a multi-component solution." *Kim* at ¶ [0222]. The "polymer possessing the negative charges is a polysulfone-based polymer containing at least one polymer selected from the group consisting of sulfonated polysulfone-based polymers and aliphatic polysulfone-based polymers." *Kim* at ¶ [0036].

In contrast, the membrane according to the present invention is based on at least one hydrophobic and at least one hydrophilic component and not comprising aliphatic or sulfonated polysulfones, which are the elements that provide the negative charges in *Kim's* membranes. *See e.g.,* new claim 34 and specification at page 9, ll. 17-27; *Kim* at ¶ [0036].

Other differences between *Kim*'s membranes and those presently claimed are further evidenced by the sieving coefficient for alpha-1-microglobulin disclosed in *Kim*, which is, on average 0.2 for *Kim*'s membranes. *Kim* at Table I. Accordingly, *Kim*'s membranes allow passage of only 20% of alpha-1-1microglobulin (MW of 25-33 kD). In contrast, IL-6 (MW of 21-29kD), and therefore within the same range of alpha-1-1microglobulin, has a sieving coefficient of 0.95. Table in Applicants' Specification at page 16; *see also* claim 12. Thus, membranes in accordance with the present claims allow passage of 95% of IL-6 molecules. Although the sieving coefficient for IL-6 is not disclosed in *Kim*, it is highly unlikely that IL-6, with an average molecular weight of 21-29kD, has a sieving coefficient of 0.9 as argued by the Office at page 3 of the Office Action.

Because the membranes in accordance with the present claims are physically different than those of *Kim*, the alleged inherent characteristics do not necessarily flow from the teachings of *Kim* to inherently anticipate the claimed membranes.

2. *Gorsuch* does not teach that molecular weight exclusion limits can "easily be manipulated"

Kim neither explicitly nor inherently anticipates the presently claimed membranes as discussed above. *Gorsuch*, which the Office contends "provides evidence in figure 7 that size exclusion limits can be easily manipulated based on the test methods used to determine size exclusion limits and sieving coefficients," fails to support the Office's assertion and also fails to remedy the deficiencies of *Kim.* Office Action, page 2. Indeed, the Office's characterization of Figure 7 of *Gorsuch* is incorrect. As pointed out in the previous Response, Figure 7 of *Gorsuch* shows exemplary curves for sieving

coefficients of different types of membranes. That is, the curves have been obtained with different membranes, and not with different test methods. In addition, the curves are not based on actual test data, but have been drawn to show the difference between high-flux membranes (left curve) and plasma separation membranes (right curve). These membranes are fundamentally different based on their composition, the processes used to prepare them, their physical structure and use. *See*, *e.g.*, the Examples in *Gorsuch*. Accordingly, the different curves do not prove how sieving coefficients can be manipulated, but rather how very different sieving coefficients are associated with various types of membranes having different compositions, methods of preparation, etc.

In addition, one of ordinary skill in the medical device art would have known that such sieving coefficients are determined by a standard for medical devices. *See e.g.,* Declaration at page 3 ("DIN EN1283 (Exhibit 3) which is the European Standard for determining various parameters of medical devices, namely haemodialysers, haemodiafilters etc."). Accordingly, determining sieving coefficients for membranes for use as medical devices are determined by a standardized protocol and not open to manipulation as the Office alleges. Therefore, Figure 7 of *Gorsuch* does not show that "molecular weight exclusion limits in water are deemed to be result effective variables," as contended by the Office. Office Action, page 2. Rather, Figure 7 merely demonstrates the differences between high-flux membranes and plasma separation membranes. Accordingly, *Gorsuch* fails to remedy the deficiencies of *Kim*. In summary, the combination of *Kim* and *Gorsuch* fails to render obvious the instant invention and Applicants respectfully request that this rejection be withdrawn.

3. Claim 34 is patentable for at least one additional reason

Claim 34 depends from claim 1 and contains, therefore, all limitations present in claim 1. Accordingly, claim 34 is patentable for at least the same reasons claim 1 is patentable. Additionally, claim 34 recites explicitly that the membrane is "an uncharged membrane." Because *Kim's* membranes are negatively charged (*see, e.g.*, *Kim* at ¶ [0036]), *Kim's* disclosure clearly fails to anticipate claim 34.

Moreover, eliminating the negative charges from *Kim's* membranes would render them unsuitable for their intended purpose because *Kim* relies on the negative charges to achieve the desired level of separation. For example, *Kim* teaches that: "in the products obtained in Examples 1-7 [corresponding to *Kim's* membranes], leaking of albumin was considerably suppressed and *fractionation performance was improved due to static repulsion of introduced negative charges*." *Kim* at ¶ [0201], emphasis added. In fact, *Kim* emphasizes the importance of the negative charges of its membranes in multiple passages throughout its specification.

Therefore, one of ordinary skill in the art would not have sought to modify Kim's membranes by removing the essential negative charges. For at least this additional reason, claim 34 is patentable over the cited art.

B. *Kim and Deppisch*

The Office rejects claim 2 under 35 U.S.C. § 103(a) as being unpatentable over *Kim* in view of "Blood Material Interactions at the Surfaces of Membranes in Medical Applications," to Deppisch et al. ("*Deppisch*"). Office Action at 3. According to the Office, *Kim* "fails to disclose the size of hydrophilic domains on the membrane surface are in the range of 20-50nm. However, the Office argues, "it is well known, as disclosed

by Deppisch, that polyvinylpyrrolidone hemodialysis membranes such as those disclosed by Kim have hydrophilic domains in the range of 20-200 nm." *Id.* The Office concludes that "[s]ince Deppisch recognizes hydrophilic domains as a result effective variable, it would have been obvious to a person having ordinary skill in the art to optimize the size of the domains as it has been held that it is not inventive to discover the optimum ranges by routine experimentation." *Id.* Applicants respectfully disagree and traverse the rejection.

Claim 2 is dependent from claim 1 and therefore encompass all the elements recited in claim 1. The shortcomings of *Kim* and *Gorsuch* have already been discussed above. *Deppisch* does not overcome these shortcomings. Rather, *Deppisch* confirms that the best membranes in the art at the time of the instant invention were recognized to require a sieving coefficient for albumin of below 0.1, thus having a molecular exclusion limit of less than 68 kD:

> The openness of the membranes is indicated by the sieving coefficients for solutes. It is dependent upon the diameter of membrane pores and the pore size distribution of the membrane. The sieving coefficients for a high flux and a low flux threelayer Polyflux S membrane measured with dextran model solutions is given in Fig. 4. The data show that the asymmetric high flux Polyflux S membrane has sieving coefficients close to the glomerular barrier in the human kidney, which is characterized by a high permeability for low- and middle-molecular weight substances, and ***a sharp cut-off minimizing albumin loss***.

Deppisch at page 244, ¶ bridging cols. 1 and 2 (emphasis added). *Deppisch*, like *Kim*, is concerned with retaining albumin or "minimizing albumin loss" using its membranes, and not allowing the retention of a portion of albumin in the presence of the whole blood, as recited in the instant claims.

Accordingly, because *Deppisch* does not remedy the shortcomings of *Kim* and *Gorsuch*, the proposed combination fails to meet the limitations of the instant claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

C. *Kim, Buck, Gorsuch* and *Kawata*

The Office rejects claims 11, 14-15, 29-31, and 33 under 35 U.S.C. § 103(a) as being unpatentable over *Kim* in view of U.S. Patent No. 4,935,141 to Buck et al. ("*Buck*") as evidenced by *Gorsuch* and European Patent No. 0 568 045 to Kawata et al. ("*Kawata*")[1] Office Action at 4. The Office contends that *Kim* "does not explicitly disclose the pore size in the separation layer," but argues that "asymmetric hollow fiber membranes having pore sizes in the range of 20-40nm are well known in the art as disclosed by Buck." *Id.* The Office further alleges that "Buck further discloses a membrane having an outer layer . . . and this outer layer is equated with applicant's fourth layer, as evidenced by the similarities between fig. 1B of Buck and fig. 4 of applicant's specification," and that *Kawata* "discloses that [the] outer surface has micropores with a 0.1-0.5 micron average pore diameter." *Id.* at 5. Applicants respectfully disagree and traverse the rejection.

Claims 11, 14-15, 29-31, and 33 ultimately depend from claim 1, and therefore encompass all the elements recited in claim 1. The shortcomings of *Kim* and *Gorsuch* have already been discussed above. *Buck* and *Kawata* do not overcome these shortcomings.

[1] Applicants note that the first named inventor for European Patent No. 0 568 045 is Kawata, and not Kagawa.

As discussed in previous Responses, *Buck*'s membranes are high-flux membranes used in standard hemodialysis, such as the P170H dialyzer analyzed in the Declaration. *See* Declaration at 5-6. *Buck*'s membranes are designed to efficiently remove molecules of a lower molecular weight and are not concerned and are not effective with removing, for example, toxic mediators having a higher molecular weight of 45kD. *Buck* expressly states that the membrane according to its invention has an exclusion limit of the size of albumin or smaller:

> [I]n accordance with the present invention, the applicants have provided a selectively permeable asymmetric membrane [...] **the substantially uniform pore openings in the first layer having a size whereby proteins which have a molecular weight of at least that of albumin are substantially completely rejected** from the membrane.

Buck at col. 1, line 67, to col. 2, line 16 (emphasis added). Since albumin has a molecular weight of 68 kDa (see *Buck* at col. 5, line 39), *Buck*'s membrane (similar to the membranes disclosed in *Deppisch*) therefore has an exclusion limit of less than 68 kD. As such, *Buck's* membranes would not have led one of ordinary skill in the art to modify them in order to arrive at the claimed invention.

In addition, *Kawata* does not remedy the deficiencies of *Kim, Buck,* and *Gorsuch*. *Kawata* describes the preparation of another high-flux membrane such as the membrane described in *Buck,* and is not concerned with the preparation of membranes for removal of high molecular weight molecules. Instead, *Kawata* is focused on an improved membrane with regards to biocompatibility. *See* Abstract; *see also* page 2, ll. 30-33.

Accordingly, because *Buck* and *Kawata* fail to remedy the shortcomings of *Kim* or *Gorsuch,* the proposed combination fails to meet the limitations of the instant claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

IV. Conclusions

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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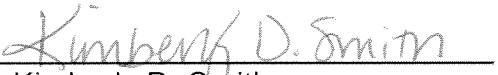
By: 
Kimberly D. Smith
Reg. No. 63,219